CONTROLLED, ORGAN SPECIFIC CHEMOTHERAPY IN PROSTATE CARCINOMA*

JUNE 10 '54

(Translated from the German at the request of [redacted])

Huguenin,[1] in a lecture on the chemotherapy of cancer called attention to the i.v. administration of diphosphoric acid ester of diethylstilbestrol for the treatment of prostate carcinoma. This substance was developed after Druckrey, Dannenberg and Schmähl[2] in new investigations proved that diethylstilbestrol (diethyldihydroxystilbene) has pronounced cytostatic properties in addition to and independent from its estrogenic action. With the previous conventional therapeutic use of stilbene derivatives in prostate carcinoma there was, however, practically no cytostatic effect since implantation and i.m. or oral administration did not lead to a sufficient concentration of the drug at the site of action. Thus, it was necessary to give diethylstilbestrol in a water-soluble, non-toxic form in high i.v. doses.

In order to utilize therapeutically the prostate acid phosphatase occurring in primary tumors as well as in metastases of prostate carcinomas, Druckrey and Raabe[3-5] suggested the manufacture of diethyldihydroxystilbenediphosphate ("ST 52-ASTA"). This substance, which is little active pharmacologically, may be given i.v. in very high doses as a so-called "transport form". The phosphate in the tumorous tissue is split by phosphatase, and the difficultly soluble, cytostatic diethyldihydroxystilbene, the so-called "active form", is liberated. Inasmuch as the prostate acid phosphatase is highly active in comparison to other phosphatases in the organism, the phosphate cleavage and liberation of stilbestrol usually occurs in the tumorous tissue, while a cleavage in other body tissues, and thus an estrogenic effect, becomes secondary. In such way, a controlled, organ specific chemotherapy becomes possible in prostate cancer.

In about 70-75% of prostatic carcinomas which are spreading into the lymphatics and metastasizing, there exists an increased serum acid phosphatase which, when the increase is distinct, confirms infiltration growth and the presence of metastases. Determination of the serum acid phosphatase is in many cases decisive for the diagnosis; it allows, by regular examination, a reliable control of the therapy. As a rule, a normalization of this phosphatase during treatment indicates, in agreement with clinical findings, the inhibition of the tumorous growth. A fall in phosphatase is usually accompanied by a conspicuous and rapid improvement of the sub-

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*Wilmanns, H.: Gezielte, organspezifische Chemotherapie beim Prostata-Karzinom, Die Medizinische, No. 1: 17-23 (1954).
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jective pains, particularly of the metastatic pains, while it takes longer to determine the retrogression of a primary tumor and of metastases. A new rise in acid phosphatase when treatment has not been continued sufficiently indicates a relapse. In contrast to Bibus,[6] it was observed frequently that a renewed rise of the acid phosphatase in the serum precedes clinical exacerbation.

In addition to the acid phosphatase, significance is given to the serum alkaline phosphatase which increases in osteoplastic bone metastases. On inhibition of the metastatic growth during estrogen therapy or cytostatic therapy with "ST 52-ASTA" there occurs an additional rise in the alkaline phosphatase as a sign of osteoplastic reparative processes. A sufficient inhibitory effect on the tumorous growth can be assumed only when the alkaline phosphatase, as well, has become normal and the acid phosphatase has also remained normal.

The treatment of prostate carcinoma with "ST 52-ASTA" was controlled in more than 7,000 phosphatase determinations carried out according to Raabe.[7] Cases, where progressing growth was indicated by an increased serum acid phosphatase, that is where the biochemical control made possible important findings, are reported in the following.

Figures 1-6 show the course of the acid phosphatase (solid curve) and the alkaline phosphatase (dotted curve). The normal region [acid phosphatase maximal to 0.5 mMU (millimol units), alkaline phosphatase to 2.5 mMU] is shaded. The case histories of these patients represent a characteristic indication for cytostatic therapy in prostate carcinoma.

J.D. (Fig. 1): Administration of estrogens since 1950; no relief from pain. Metastasis was unavoidable. In August 1952, with existing pelvic and glandular metastases and a very high serum acid phosphatase, treatment was started with "ST 52-ASTA". As is apparent from the graph, the patient responded promptly 4 times to an intensive treatment with daily i.v. injections; however, a relapse --signified by a renewed rise of the serum acid phosphatase-- occurred every time this treatment was not followed up by long-term therapy. Even an estrogen treatment in February 1953 could not prevent the relapse. The fourth intensive treatment with "ST 52-ASTA", in April 1953, was followed up with 2 injections (250 mg./inject.) a week. Accompanied by slow improvement of the general condition, the biochemical finding is now, for the first time, normal since six months.

J.M. (Fig. 2): Here, too, long-term therapy was necessary. In November 1952 --with strongly increased serum acid phosphatase-- good clinical and biochemical reaction to an intensive therapy with 24 injections "ST 52-ASTA". Complete freedom from pain and general improvement were the reason to discontinue the treatment so that a relapse occurred in January/February 1953. In this case, too, the serum acid phosphatase was markedly increased before subjective and objective exacerbation was observed.

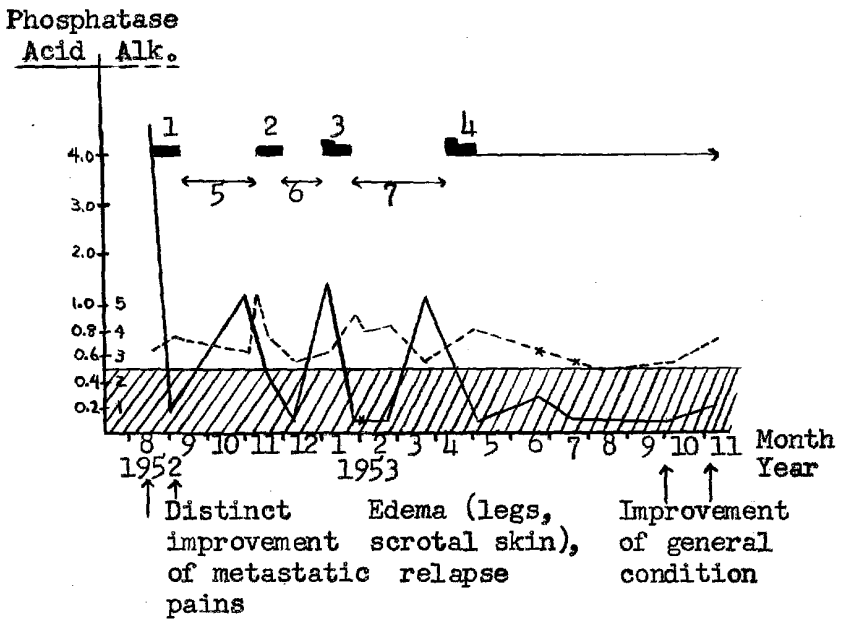
Renewed treatment with daily injections of "ST 52-ASTA" (500 mg., daily, for 5 days, followed by 250 mg., daily for 15 days) rapidly effected a normalization of the acid

phosphatase and freedom from pain. With additional administration of estrogenic substances (depot agents), a lasting inhibition of the tumorous growth was manifest within an observation period of 8 to 9 months. No pain whatsoever. All check-ups show a normal serum acid phosphatase.

Figure 1

J.D., 49 years

Estrogen treatment since March 1950 (pelvic and glandular metastases)

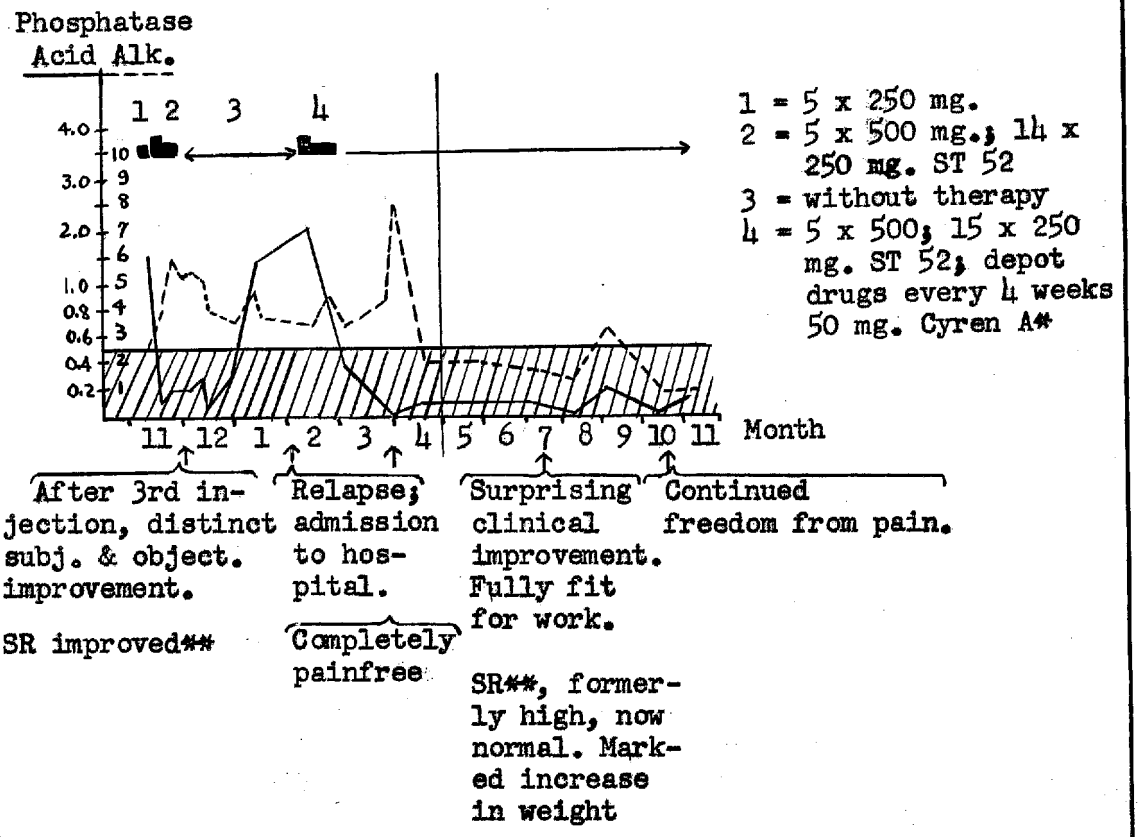


1 = 15 x 250 mg. Aug. 29 - Sept. 18
2 = 250 mg. Nov. 3-15
3 = 5 x 500, 12 x 250 mg. Jan. 6-23
4 = 5 x 500, 15 x 250 mg. ST 52
250 mg. twice a week
5 = without therapy
6 = without therapy
7 = Cyren, Plenosol*

*Plenosol (Dr. Madaus & Co., Köln) = an extract from Viscum album, biologically standardized. Indications: inoperable cancer.

Figure 2

J. M., 51 years

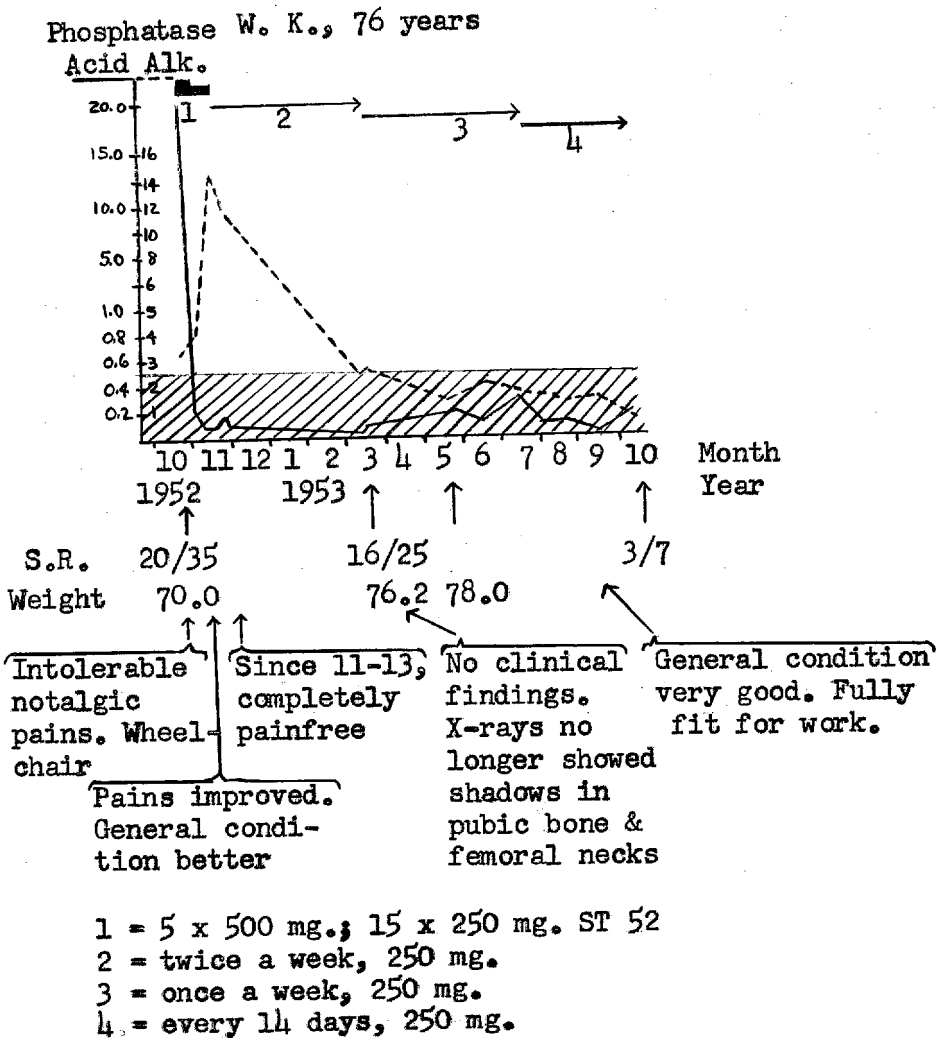


W. K. (Fig. 3): In October 1952, patient was admitted to hospital with intolerable notalgia. X-ray studies showed bone metastases of a prostate carcinoma. A very high serum acid phosphatase confirmed the diagnosis. This condition necessitated the administration of opiates. After intensive treatment with "ST 52-ASTA" (daily injections for 20 days) distinct clinical and biochemical improvement. Notalgic pains improved after a few days, disappeared completely on Nov. 13th. The serum acid phosphatase normalized within a short time and, with subsequent treatment carried out regularly, remained normal up to the present time. The maintenance dose consisted of individual "ST 52-ASTA" injections of 250 mg./inject. (until March 1953, 2 x a week; then once a week until July; at the present time, in intervals of 2 weeks). The characteristic rise in serum alkaline phosphatase at the beginning of the therapy and its slow normalization are significant. The course of the blood sedi-

*Cyren A (Bayer, Leverkusen) = diethylhydroxystilbene. Indication: in cancer of the prostate.
**SR = sedimentation rate.

mentation, as well, which was still slightly accelerated in March and completely normal in October, indicates that final inhibition of the tumorous growth sets in only gradually. In March, x-rays showed that the spherical osteoplastic foci in the ischium were no longer distinct, and that there were no longer any traces of shadows in the pubic bone and the femoral necks. The patient's general condition (age 76) has been excellent for months and his working ability is fully restored (garden and field work). The prostate carcinoma can no longer be established clinically.

Figure 3



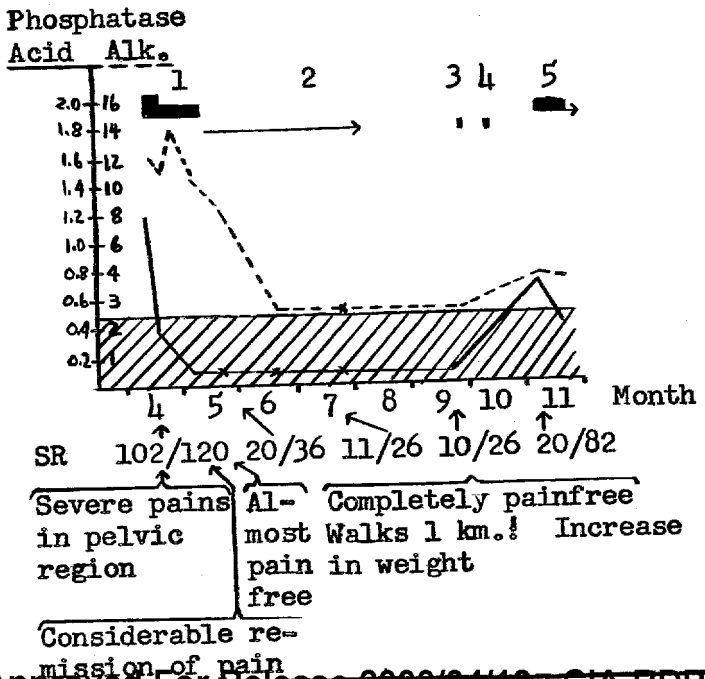
J. B. (Fig. 4): Since the beginning of 1952, patient was treated with 2 injections/week of depot-estromone. A severe swelling of the mammary glands was a criterion that the therapy was carried out in the best possible manner. Despite this fact, there was no inhibition of the tumorous growth (high serum acid phosphatase, severe metastatic pains). Intensive treatment with "ST 52-ASTA" in April/May 1953 (500 mg. daily for 6 days, followed up by 250 mg. daily for 21 days) rapidly effected a normalization of the serum acid phosphatase, complete freedom from pain, considerable improvement of physical efficiency, increase in weight, decrease of blood sedimentation from 102/120 mm. to 20/36 mm. A suggested continuation of the therapy with 2 injections/week (250 mg. each) of "ST 52-ASTA" was not carried out regularly since patient lacked sufficient insight into his illness. Since July 31, 1953, only 2 more individual injections of "ST 52-ASTA" at 250 mg. each (on Sept. 29 and Oct. 13), which were of little therapeutic value. While the biochemical check-up in September showed a normal serum acid phosphatase, both phosphatases were markedly increased on Nov. 3 as a sure sign of growing osteoplastic bone metastases. The blood sedimentation, as well, was strongly accelerated again. However, the general condition of the patient still did not indicate a relapse. After readmission to hospital, renewed therapy with daily injections of "ST 52-ASTA" rapidly effected a fall in the serum acid phosphatase and blood sedimentation.

This observation is particularly important since it proves that long-lasting effects with "ST 52-ASTA" can be obtained even in cases where conventional hormone- and estrogen-treatments are ineffective, but that on the other hand, a subsequent, continued therapy is indispensable for a permanent inhibition of the tumorous growth.

Figure 4

J. B., 71 years

For 1 year depot-estromone twice a week; severe swelling of mammary glands!



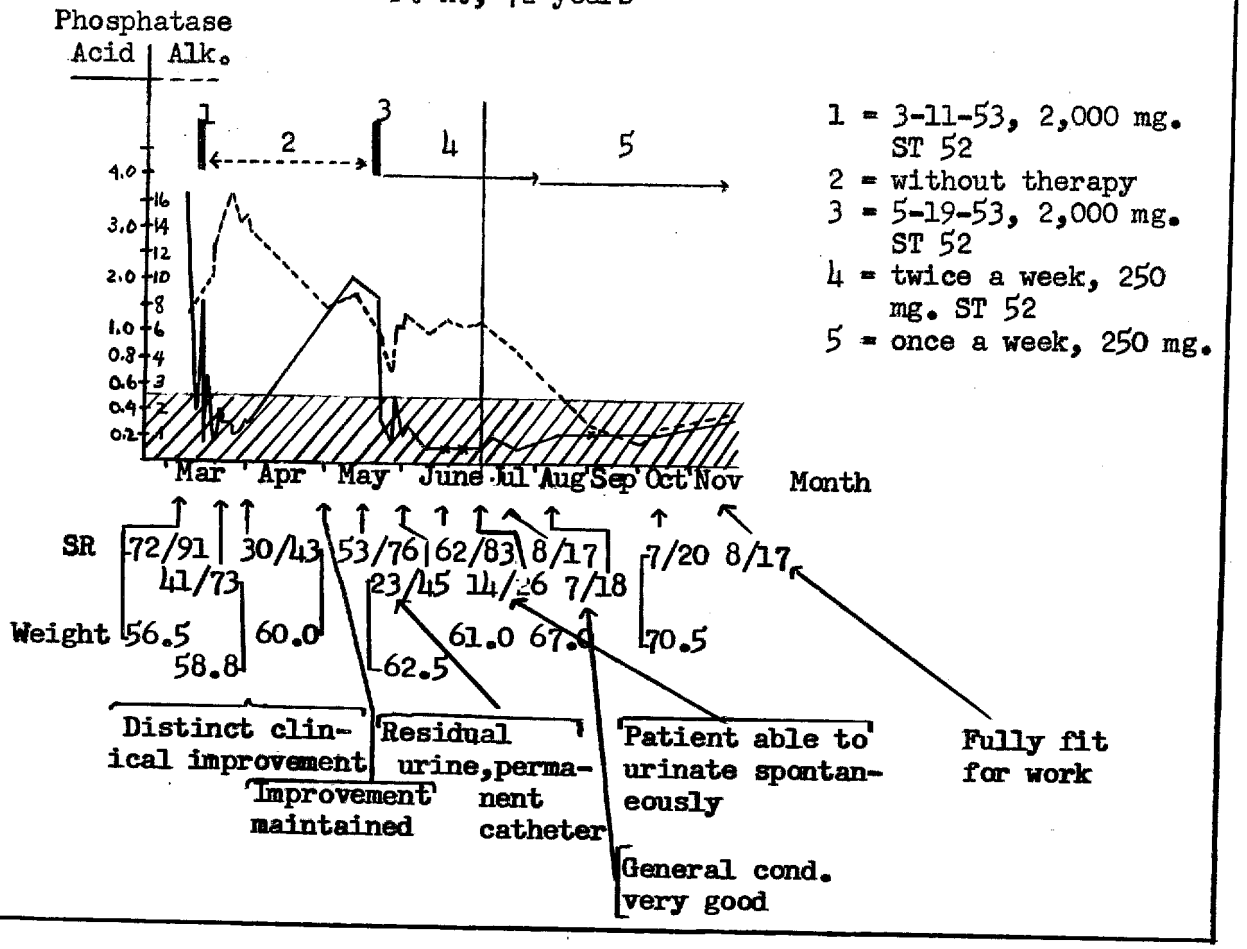
1 = 6 x 500, 21 x 250 mg. ST 52
2 = weekly 1-2 x 250 mg. ST 52
3 = 250
4 = 250 mg.
5 = daily 250 mg.

F. H. (Fig. 5): Since the therapy with daily i.v. injections is often difficult to carry out, a massive dose with the maximal amount of "ST 52-ASTA" was attempted. Moreover, it is theorized that the activity of the prostate acid phosphatase in the tumorous tissue is reduced as a consequence of the cytostatic therapy. As demonstrated in Fig. 5, patient H reacted very favorably to a single dose of 2,000 mg. "ST 52-ASTA" on March 11, 1953. The acid phosphatase, which showed some fluctuations during the first days, was completely normal on the 5th day after injection; almost daily controls until release from hospital on March 31, 1953. Distinct clinical improvement. Absolute freedom from pain. No further treatment. It is significant that the blood sedimentation of 30/43 on the patient's release from the hospital showed distinct improvement as compared to 72/91 on his admission; however, it was by no means normalized. The serum alkaline phosphatase also was still very high. Thus, it cannot be assumed that the tumorous growth is inhibited sufficiently.

A biochemical test on April 30, 1953 revealed a considerably increased acid phosphatase in the serum as the first sign of relapse. Clinical exacerbation is not yet ascertainable at this time. There are no subjective pains. Two weeks later, renewed disturbance of miction.

Figure 5

F. H., 72 years

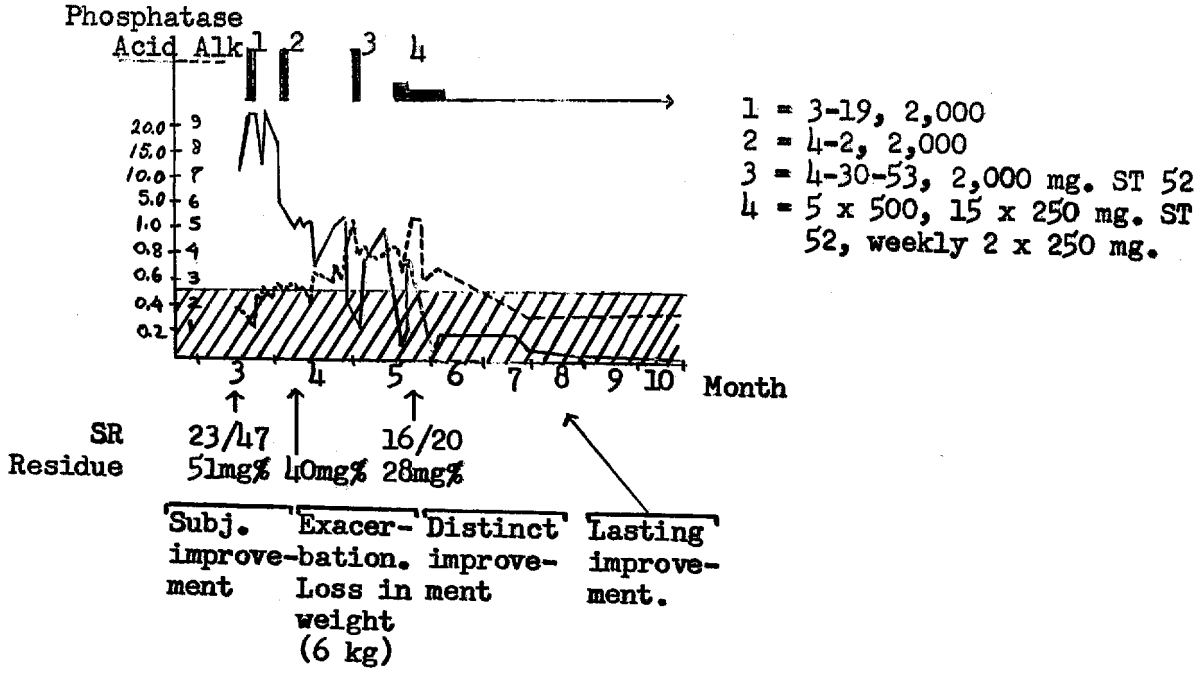


An additional massive dose of 2,000 mg. "ST 52-ASTA" effected rapid clinical and biochemical improvement. Ten days after injection the patient is able to urinate spontaneously. Continued treatment with 2 injections/week of "ST 52-ASTA" (250 mg./inject.), and one injection per week since August 1, led to a lasting inhibition of the tumorous growth and, in the course of four months, to a normalization of the blood sedimentation and serum alkaline phosphatase.

F. A. (fig. 6): Massive dose therapy. Three injections of 2,000 mg./inject. "ST 52-ASTA" acted insufficiently on the serum acid phosphatase which increased again rapidly after the third injection. No startling clinical improvement. In May 1953, intensive therapy with daily injections of "ST 52-ASTA" which caused rapid normalization of the acid phosphatase. Under continued treatment of 2 injections per week at 250 mg./inject., the biochemical finding has been normal for the past five months. Lasting improvement of patient's general condition.

Figure 6

F. A., 65 years



"ST 52-ASTA" is well tolerated in general. Normally, there occur severe sensations (i.e., stinging, itching and pains) during and immediately after injection; in some cases, pain reactions were reported in the metastatic region. However, these subjective symptoms usually disappear very quickly, often after a few minutes, sometimes after 20-30 minutes. No detrimental effects on the hemogram. On the contrary, secondary anemias conditioned by a spreading of the carcinoma frequently improved in the course of a long-term therapy. No damage to internal organs. No pathological findings in liver function tests.

Gynecomastia and other female characteristics in men were observed only in rare cases after "ST 52-ASTA". This experience shows that the estrogenic effects of diethyldihydroxystilbenediphosphate, administered i.v., recede into the background when compared to the cytostatic properties of the substance. If the hormonal effect is lacking or only slight, one cannot count on a reactive hypersecretion of androgenic principles from the adrenal cortex after administration of "ST 52-ASTA".

The estrogens, on the other hand, cause inhibition of the testicles which, as a consequence, via the hypophysis, leads to a compensatory excess secretion of androgenic hormones from the adrenal cortex. However, since the androgens promote the growth of prostate carcinoma, the relapses occurring during long-term therapy are explained by hyperplasia and exaggerated function of the adrenal cortex.[8-11] This clarifies the fact that a permanent cure is not observed after the administration of estrogens. The lack of a pronounced hormonal action in the cytostatic therapy of prostate carcinoma with "ST 52-ASTA" is also an advantage from this point of view.

Table 1 shows the results so far obtained with the "ST 52-ASTA"-therapy in 161 patients suffering from metastasizing, progressing prostate carcinoma, whose serum acid phosphatase was increased before undergoing treatment. The acid phosphatase was normalized in 90 patients. This number contains 27 cases that were pretreated with estrogenic substances, or where the carcinoma had been existing for one or several years. With 33 patients, on the other hand, the serum acid phosphatase was not normalized completely and 38 additional patients could not be influenced biochemically. Both of these groups contain 21 cases each where the treatment was not carried out correctly as experiences now show (i.e., insufficient dosage, interruption of therapy). These two groups include 27 cases where carcinoma existed for more than one year, or where pretreatment was carried out with estrogenic substances for the same length of time. Clinical improvement in 11 of the 38 patients who could not be influenced biochemically.

The tabular summary shows that "ST 52-ASTA" is administered successfully also in patients who have not responded to the standard estrogen treatment.

Table 1

Results of "ST 52-ASTA"-treatment obtained in 161 patients with metastasizing prostate carcinoma.

	Total number of cases		Old and pretreated cases	
		Clinically improved		Clinically improved
I. Acid phosphatase normalized	90	87	27	27
II. Acid phosphatase influenced — but not normal	33	9	9	5
a) with sufficient dosage	12	6	5	2
b) with insufficient dosage	21	3	4	3
III. Acid phosphatase not influenced	38	2	18	2
a) with sufficient dosage	17	2	8	2
b) with insufficient dosage	21		10	
Total	161	98	54	34

The decisive factor for good results is a very intensive initial therapy. With rapidly growing carcinomas, particularly where malignant growth has been progressing over a long period of time and with patients pretreated with estrogen, a long-term therapy is necessary with daily injections of high doses. As a guide for the administration of "ST 52-ASTA", the author recommends slow i.v. injection of 500 mg., daily, for 5-10 days, followed by 250 mg., daily, for the next 10-20 days. Depending on clinical and biochemical findings in given cases, the therapy may have to be prolonged even more.

The second prerequisite for good results and for a truly lasting inhibition of the tumerous growth is uninterrupted continuation of the therapy, even after clinical and biochemical remission is obtained. Depending on the patient's reaction, 1-3 injections of "ST 52-ASTA" per week are sufficient. If there are no relapses within a longer period of observation, the time intervals between the individual injections can be extended.

A massive dose therapy with very high doses (2,000 mg.) is recommended only for patients whose general condition is good and the metastases not too widespread, since otherwise toxic side effects (e.g., severe vomiting) may occur as a result of disintegration products of the tissue.

The therapy should be checked in every case by serum phosphatase examinations at regular intervals; in this way it is possible to form an opinion about the inhibition of the tumorous growth; besides, continuous biochemical control may also give valuable hints for additional treatment of each individual case. In order to avoid misunderstandings, it should be re-emphasized that the method of phosphatase control can be used only to determine metastasizing and infiltrating prostate carcinomas. In non-metastasizing prostate carcinomas, phosphatase determinations should be carried out at intervals of 1 to 2 months so that, in given cases, spreading of cancer can be recognized in time.

Summary

The controlled, organ specific chemotherapy in prostate carcinoma with diethyldihydroxystilbenediphosphate ("ST 52-ASTA") is superior to the standard estrogen therapy.

With an intensive initial treatment, and with controlled permanent therapy, it is possible to achieve lasting inhibition of the tumorous growth and clinical improvement to the extent that all symptoms disappear.

The advantage of the controlled, organ specific chemotherapy in prostate carcinoma lies in its high intensity of action on the tumorous tissue, while it does not damage other proliferative cell systems of the organism. Feminization is observed only in rare cases after i.v. therapy with "ST 52-ASTA".

The acid and alkaline phosphatases in the serum are of great importance for the diagnosis of metastasizing prostate carcinomas. Their determination at regular intervals is of particular value for a controlling of the therapy.

References

1. Huguenin, R. and Truhaut, R.: 7th International Congress of Radiology. Actions de la chimiotherapie dans le traitement des cancers humains.
2. Druckrey, H., Danneberg, P. and Schmähl, D.: Naturwiss. 39:381 (1952).
3. Druckrey, H., and Raabe, S.: Klin. Wschr. 30:882 (1952).
4. Druckrey, H.: Dtsch. med. Wschr. 77:1495,1534 (1952).
5. Druckrey, H.: Die Medizinische 1025, 1953.
6. Bibus, B.: Schweiz. med. Wschr. 83:373 (1953).
7. Raabe, S.: Langenbecks Arch. u. Dtsch. Z. Chir. 273:373 (1953).
8. Alyea, E. P.: J. Urolog. 53:143 (1945).
9. Huggins, C.: Science 97:541 (1943); Canad. M. A. J., 50:301 (1944).
10. Mortensen, H.: Med. J. Australia 40:278 (1953).
11. Smith, P. G., Rush, T. W. and Evans, A. T., J. Urolog. 65:886 (1951).

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